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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/031,801	03/15/1993	RAJU KUCHERLAPATI	A-CELL-4.4-U	1945

7590 03/13/2002

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EXAMINER

BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/13/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

08/031,801

Applicant(s)

KUCHERLAPATI ET AL.

Examiner

Anne M Beckerleg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 December 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 83-88,95-97 and 104-109 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 83-85 is/are allowed.
- 6) ☒ Claim(s) 86-88,95-97 and 104-109 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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### **DETAILED ACTION**

The applicant's response and terminal disclaimer received on 12/27/01 have been entered. This application contains claim 68 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 83-88, 95-97, and 104-109 are under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

### ***Double Patenting***

The rejection of claim 83 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 -5 of U.S. Patent No. 6,114,598, 9/5/00, is withdrawn in view of applicant's terminal disclaimer, filed on 12/27/01, which has been deemed proper and entered into the record of the instant application.

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***Claim Rejections - 35 USC § 112***

The rejection of claims 86-88, 95-97, and 104-109 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for the reasons of record as discussed in detail below.

The applicant argues that the specification provides sufficient guidance for YACs which include at least 5 VH genes and that applicant's amendment to the claims now limits the VH genes to those found on human chromosome 14. The claims as amended continue to read broadly on germline segments of the Ig heavy or light chain locus including the D segment and J segment genes and the C $\mu$  constant region operably linked to one or more human V segment genes which can include the entire Ig locus minus the switch regions and constant regions 3' of the C $\mu$  gene. The specification does not provide sufficient guidance concerning the construction of YAC vectors including additional V segments up to and including the entire V region of either the heavy or light chain loci. At the time of filing, physical mapping, cloning, and sequencing of the entire human heavy chain variable locus had not been accomplished. In addition, as late as 1993, the actual number of functional V segment genes was unknown and complicated by the presence of large numbers of non-functional pseudogenes (Matsuda et al.). The specification provides no guidance as to the sequence of variable regions distal to the D heavy chain region on chromosome 14. The specification further does not provide guidance for obtaining YACs which

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include the germline sequence of chromosome 14 that comprises variable regions genes other than the first few V region genes directly adjacent to the D region, or provide guidance for functional heavy chain variable gene sequences which could be linked to the germline sequence shown in Figure 16. Thus, the specification fails to teach how to make a YAC or any other vector which comprises the germline sequence of chromosome 14 including the entire D region and J region genes, the C $\mu$  region, and any or all variable region genes.

In regards to the additional YACs referred to by the applicant on page 56-59 of the specification, the 205 kb YAC contains a deletion that removes some of the D gene cluster, while the 215 kb YAC has a deletion that removes the mu gene. Thus, neither of these YACs meets the limitations of the applicant's claims which recite a DNA sequence identical to or which contains a germline DNA sequence of human chromosome 14 from the D segment genes through the J segment genes and the constant region genes through C $\mu$ .

In regards to the 230 kb pair YAC disclosed on page 59 of the specification as the A287-C10 YAC, the specification does describe a A287-C10 YAC which apparently contains the 5 V region heavy chain genes which are immediately adjacent to the D region genes, the complete D region genes, the complete J region, and C $\mu$ . However, the heavy chain V region by itself is greater than 1 megabase in size. The isolation of a single YAC containing a contiguous piece of genomic human genomic DNA encoding 1 variable region gene, D, J, and C $\mu$ , and a single YAC containing 5 variable region genes, D, J, and C $\mu$ , does not enable the isolation and genetic manipulation of YACs containing even a quarter or more of the variable region genes, let alone

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the entire V gene repertoire found on human chromosome 14. Furthermore, the Cox declaration, as discussed in previous office actions, clearly teaches that YACs containing larger regions of the human heavy chain locus, such as the NotI fragment disclosed in the instant specification, are in fact unstable. In addition, the claims continue to read on making and using genetic constructs encoding the entire genomic light chain locus from any and all non-murine species. As noted in previous office actions, the specification completely fails to provide any guidance for the genomic light chain loci of any species other than human. Furthermore, the specification only provides guidance for the human kappa light chain locus, and specifically for YACs which contain only the first few human kappa light chain V region genes most proximal to the human light chain D region. The specification fails to provide sufficient guidance for YACs or other types of genetic constructs which encode distal human variable region genes or which encodes the human variable region genes in their entirety.

Further, as noted in previous office actions, the specification of the instant application regarding the actual production of transgenic mice containing human immunoglobulin genes or immunoglobulin genes from any other non-murine species using spheroplast fusion is speculative and does not present any working examples which demonstrate the production of transgenic mice which express human heavy chains and in addition human or non-murine light chains. Therefore, in view of the lack of teachings in both the art and the specification for the complete sequence of the functional V segment genes on chromosome 14, the lack of guidance for operably linking nucleotide sequences encoding V genes distal to the D heavy region, the art recognized instability

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of YACs comprising large segments of human chromosome 14, the lack of guidance for any non-murine genomic light chain loci other than the human loci, the lack of working examples which demonstrate transgenic mice which actually express human heavy chains, and optionally any non-murine light chain, and the breadth of the claims, the skilled artisan would not have predicted success in obtaining a YAC or any other DNA sequence encoding the human germline D region, J region, and C $\mu$  gene operably linked to any or all human V segment genes and as such it would have required undue experimentation to produce the transgenic mice as claimed.

Claims 86-88, 95-97 and 104-109 stand rejected under 35 U.S.C. 112, first paragraph, for lack of written description. The applicant has treated the rejection of the claims under 112, for lack of enablement, and the rejection of the claims under 112, for lack of written description, together. The arguments presented by applicants under the heading of 112 are therefore apparently intended to apply to both rejections, even though the rejections are in fact separate rejections (see *Vas-Cath*). Applicant's arguments as presented have been fully considered and addressed in depth above in the section regarding the rejection of the claims under 112, first paragraph, for lack of enablement. Therefore, the rejection is maintained for reasons of record as detailed above and as found in paper no. 50.

Claims 83-85 are considered allowable over the prior art of record.

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**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg



**A.M.S. BECKERLEG**  
**PATENT EXAMINER**